[19] State Intellectual Property Office of P.R.C.

[51] Int. Cl[7]
A61K 38/34
//(A61K38/34,31:55)

[12] Publication of Specification for Patent Application

[21] Application No. 99112768.4

[43] Publication Date: September 27, 2000

[11] Publication No. CN1267548A

[22] Filing Date: 1999.3.18 [21] Application No. 99112768.4

[71] Applicant: Hu, Xiu-Yun
Address: An-Shan Second Hospital, No. 58, W. Jie-Feng Rd., An-Shan City, 114014 Liao-Ning
Joint Applicants: Chin, Chun; Ding, Xiao-Wei
[72] Inventor: Hu, Xiu-Yun; Chin, Chun; Ding, Xiao-Wei

[74] Patent Agent: An-Shan Re-Neng Patent Agent
Attorney: Chang, Chun

Claims: 1 Page; Specification: 4 Pages; Drawing: 0 Page

[54] Title of the Invention:

A PHARMACEUTICAL COMPOSITION COMPRISING MELATONIN AND DIAZEPAM FOR SLEEP REGULATION

[57] Abstract

A pharmaceutical composition comprising melatonin and diazepam for sleep regulation is disclosed. The pharmaceutical composition is characterized in containing melatonin and diazepam in a ratio ranging between 1:0.1 and 1:50 and containing starch as an excipient of between 94% and 96 relative to the total weight of the pharmaceutical composition. To produce the pharmaceutical composition, the above melatonin, diazepam, and starch in proportion are ground, mixed, sieved with a100-mesh screen, and encapsulated as capsules or compressed into tablets for oral administration. The pharmaceutical composition is advantageous for providing excellent hypnotic effect without the after effect known as brought by diazepam.

CLAIMS

1. A pharmaceutical composition comprising melatonin and diazepam for sleep regulation, characterized in containing melatonin and diazepam in a ratio ranging between 1:0.1 and 1:50 by weight and containing starch as an excipient of between 94% and 96 relative to a total weight of the pharmaceutical composition; and

made by:

mixing ground melatonin, diazepam, and the starch in proportion as a mixture, sieving the mixture with a100-mesh screen, and encapsulating the sieved mixture into capsules or compressing the sieved mixture into tablets so as to obtain an oral preparation.

2. The pharmaceutical composition of Claim 1, wherein the ratio between melatonin and diazepam ranges between 1:5 and 1:50.

3. The pharmaceutical composition of Claim 2, wherein the ratio between melatonin and diazepam is 1:5.

SPECIFICATION

A PHARMACEUTICAL COMPOSITION COMPRISING MELATONIN AND DIAZEPAM FOR SLEEP REGULATION

The present invention is related to a pharmaceutical composition and more particularly, to a pharmaceutical composition comprising melatonin and diazepam for sleep regulation.

Diazepam has been clinically applied as a sedative-hypnotic drug for years. While being proven as effective in sleep regulation, diazepam can bring after effect associated with next-morning somnolence and prolonged sleepiness, which is still an unsolved issue to clinical medication. Melatonin, as the major hormone secreted from pineal gland, functions crucially in information transmission, particularly in photoperiodic signal transmission, between organisms and environments. Melatonin facilitates modulating function rules inside organisms by synchronizing the rules with the environmental photoperiod, thereby regulating organismic sleep-wake cycle without after effect of hypnotic drugs. For enhancing the application of melatonin, which has shown significant market potential as a functional food, a series of melatonin derivatives for sleep regulation was introduced by China Patent No. CN1107701A.

Basing on the prior art, the present invention has an objective to propose a pharmaceutical composition comprising melatonin and diazepam for sleep regulation, by composing the pharmaceutical composition with the optimal formulation so as to provide the pharmaceutical composition facilitating sleep regulation as a clinical sleep-regulation drug.

The technical summary of the present invention will be given below:

The pharmaceutical composition comprising melatonin and diazepam for sleep regulation is characterized in containing melatonin and diazepam in a ratio ranging between 1:0.1 and 1:50 by weight, preferably between 1:5 and 1:50, and most preferably between 1:5, while containing starch as an excipient of between 94% and 96 relative to a total weight of the pharmaceutical composition.

The pharmaceutical composition is made by:

mixing ground melatonin, diazepam, and the starch in proportion as a mixture, sieving the mixture with a100-mesh screen, and encapsulating the sieved mixture as capsules or compressing the sieved mixture into tablets for oral administration.

The pharmaceutical composition has advantages of:

providing improved hypnotic effect without brining after effect.

According to one embodiment of the present invention, to prepare the

pharmaceutical composition, 1.0g of melatonin, 5.0g of diazepam, and 6g of starch as an excipient are ground and mixed in a mill. Then another 6g of starch is added to and mixed with the resultant mixture. The previous step shall be repeated until the total 230g of starch is completely consumed. Afterward, the resultant mixture is sieved with a100-mesh screen and encapsulated into 1000 #2-capsules.

The experiments given below were conducted by using the formulation of the above pharmaceutical composition.

I. Biological Activity Experiment

1. Materials and Method

1) Test Substances:

Melatonin capsules containing a melatonin content of 1 mg/capsule obtained from Dalian Fei-Suo Group were solved in distilled water before use. Diazepam tablets from Chifeng Pharmaceutical Co. were used.

2) Animal Subjects:

Kunming mice (half males and half females) were provided by Animal Room, China Medical University. Each said mouse was 20±1g.

2. Experiment Method

One hundred and sixty (160) mice were randomly grouped into 16 groups, each including 10 mice. The mice in the 1st group were administrated by pouring into stomach (ig) with 10ml/kg of distilled water. The mice in the 2nd to the 4th groups were administrated by pouring into stomach (ig) with 0.5 mg/kg, 1 mg/kg, and 10mg/kg of melatonin, respectively. The mice in the 5th to the 7th groups were administrated by pouring into stomach (ig) with 1 mg/kg, 5 mg/kg, and 25 mg/kg of diazepam, respectively. The mice in the 8th to the 10th groups were administrated by pouring into stomach (ig) with 0.5 mg/kg of melatonin together with 1 mg/kg, 5 mg/kg, and 25 mg/kg of diazepam, respectively. The mice in the 11th to the 13th groups were administrated by pouring into stomach (ig) with 1 mg/kg of melatonin together with 1 mg/kg, 5 mg/kg, and 25 mg/kg of diazepam, respectively. The mice in the 14th to the 16th groups were administrated by pouring into stomach (ig) with 10mg/kg of melatonin together with 1 mg/kg, 5 mg/kg, and 25 mg/kg of diazepam, respectively. The capacity was 10ml/kg in all cases. After 30 minutes since the administration, the mice's activity was observed by checking the righting reflex and sleep state. The lab temperature was kept at 27-28°C.

3. Results

The three groups of mice that received only melatonin reduced activity and turned into a sedated state after 30 minutes since the administration. The result indicates that the three applied dosages of melatonin are all minimal dosages for hypnogenesis. The three groups of mice administrated with three different dosages of

diazepam all reduced activity gradually while the mice in the group receiving 0.5 mg/kg of diazepam did not fall into sleep but those receiving 5 mg/kg and 25 mg/kg of diazepam did (as shown in Table 1). The conjunct use of melatonin and diazepam led the mice in all groups to sleep for different durations. Particularly, even the mice in the group receiving the minimum dosages of both melatonin and diazepam lost the righting reflex, indicating that the combination of melatonin and diazepam exactly improved the hypnotic effect. The other groups receiving the combination in different ratios also showed sleep durations longer than those of the groups receiving the same dosages of diazepam. Therein, the melatonin-to-diazepam ratios of 1:25 and 10:25 showed the most impressive results. Through analysis of variance, all of the comparisons between the groups receiving the combination and the comparison group reached statistical significance. Melatonin dominated between the two elements of the combination while among three dosages of melatonin, 1 mg/kg and 10 mg/kg did not show remarkable difference. After comparative selection, it was determined that the preferred melatonin-to-diazepam ratio ranges between 1:5 and 1:25, while the most preferred melatonin-to-diazepam ratio is 1:5.

Group	Melatonin (mg/kg)	Diazepam (mg/kg)	Sleep Duration (minute)
Comparison Group	--	--	0
Melatonin	0.5	--	0
Melatonin	1	--	0
Melatonin	10	--	0
Diazepam	--	1	0
Diazepam	--	5	6.9±7.1
Diazepam	--	25	39.5±17.4
Melatonin+ Diazepam	0.5	1	18.4±11.7
Melatonin+ Diazepam	0.5	5	69.8±21.7
Melatonin+ Diazepam	0.5	25	125.6±28.3
Melatonin+ Diazepam	1	1	74.6±25.9
Melatonin+ Diazepam	1	5	177.8±31.6
Melatonin+ Diazepam	1	25	199.1±57.2
Melatonin+ Diazepam	10	1	85.5±21.8
Melatonin+ Diazepam	10	5	183.1±38.5
Melatonin+ Diazepam	10	25	201.4±45.7

Table 1. Mice Sleep Duration (X±SD) Cause by Melatonin and/or Diazepam

III. Human Trial Experiment

Fifteen (15) volunteers of ages between 30 and 45 were picked among the staff of some hospital and verified as having no any other disease. The volunteers were requested to stop taking other drugs during the experiment. Every volunteer orally took 1mg of melatonin and 5 mg of diazepam each day before sleep for consecutive ten days. After the ten days, the volunteers' subjective responses were collected. All of the 15 volunteers experienced better sleep quality and less dreaming after taking the combination, and none of the 15 volunteers experienced next-morning weakness or sleepiness. The results indicate that the combination of melatonin and a lower dosage of diazepam facilitates better sleeping without brining the side effect of diazepam.

Toxicity Experiment

1. Method

Melatonin and diazepam are mixed in proportion and dissolved in distilled water to form a melatonin-diazepam solution of the maximally available concentration. 40 mice containing 20 males and 20 females were randomly grouped into 2 groups and administrated with the solution in the maximum concentration and the maximum allowable volume, respectively. The dosages applied were up to 10mg/kg of melatonin and 50mg/kg of diazepam, and the mice's activity change and poisoning characteristic for the sequent 14 days.

2. Results

After 15 minutes since taking the solution, the mice started to reduce activity and fell into sleep. The mice lost the righting reflex for 5 hours and then gradually recovered. Through the sequent 14 days, no change was observed. The results suggest that the combination applied with a normal dosage is safe.

[19]中华人民共和国国家知识产权局

[51]Int.Cl⁷
A61K 38/34
//(A61K38/34,31:55)

[12]发明专利申请公开说明书

[21]申请号 99112768.4

[43]公开日 2000年9月27日

[11]公开号 CN 1267548A

[22]申请日 1999.3.18 [21]申请号 99112768.4

[71]申请人 胡秀云
地址 114014 辽宁省鞍山市西鲜放路58号鞍山市第二医院
共同申请人 秦 群 丁晓维
[72]发明人 胡秀云 秦 群 丁晓维

[74]专利代理机构 鞍山热能专利事务所
代理人 张 群

权利要求书1页 说明书4页 附图页数0页

[54]发明名称 一种由褪黑素和安定制成的调节睡眠的组合物

[57]摘要

本发明公开了一种由褪黑素和安定制成的调节睡眠的组合物。特征是该组合物 中褪黑素和安定的比例为1:-0.1—50,加入制剂淀粉占总量的94—96%;制作方法是:按比例称取褪黑素、安定、制剂淀粉研磨混合均匀,将混 合均匀的细粉过100网目筛,装入胶囊或压片得口服制剂。优点是:此药物 组合物有良好催眠作用,克服了单独应用安定的后遗效应的缺点。

ISSN1008-4274

权 利 要 求 书

1．一种由褪黑素和安定制成的调节睡眠的组合物，其特征在于：该组合物中褪黑素和安定的比例为1:0.1-50(重量比，以下同)，加入制剂淀粉占成品药物的94—96%；

其制作方法是：

按比例称取褪黑素、安定、制剂淀粉研磨混合均匀，将混合均匀的细粉过100网目筛，装入胶囊或压片即得口服制剂。

2．根据权利要求1所述的褪黑素和安定制成的调节睡眠的组合物，其特征在于：其中的较佳比例范围是1:5-50。

3．根据权利要求2所述的褪黑素和安定制成的调节睡眠的组合物，最佳比例是1:5。

说　明　书

一种由褪黑素和安定制成的调节睡眠的组合物

本发明涉及一种药物组合物，特别是一种由褪黑素和安定制成的调节睡眠的组合物。

安定是临床应用多年的镇静催眠药，有肯定的睡眠调节作用，但服用该药后常常引起后遗效应，造成用药次晨嗜睡，困意不消，是困扰临床多年而始终未能解决的课题。褪黑素(Melatonin)是松果腺分泌的主要激素，在机体与环境之间信息传递特别是光周期信号的传导过程中起关键作用。褪黑素可以调整机体功能内在运行规律，使其与环境周期同步，因而对睡眠一觉醒周期具有调节作用，而不表现出催眠药的后遗效应。作为保健食品褪黑素在世界上有很好的市场，为了更好发挥褪黑素的应用潜力，中国专利CN1107701A公开了一系列褪黑素衍生物，用于调节睡眠。

本发明的目的是提供一种由褪黑素和安定制成的调节睡眠的组合物，用最佳配比，使其具有调节睡眠作用，为临床提供一种调节睡眠药物。

本发明技术内容简述如下：

一种由褪黑素和安定制成的调节睡眠的组合物，其特征在于：该组合物中褪黑素和安定的比例为1:0.1-50(重量比，以下同)。其中的较佳比例范围是1:5-50，最佳比例是1:5，加入制剂淀粉占成品药物的94—96%。

其制作方法是：

按比例称取褪黑素、安定、制剂淀粉研磨混合均匀，将混合均匀的细粉过100目筛，装入胶囊或压成片即得口服制剂。

本发明的优点是：

有较好的催眠效果，服用后无后遗效应。

将褪黑素1.0克、安定5.0克与6克淀粉放入乳钵内研磨混合，再取等量淀粉与已混药物研磨混合，依此类推，顺次增加淀粉量与已混药物

研磨混合直到230克淀粉用完为止。过100网目筛，装入2号胶囊中共制1000粒。

下面结合实施例给出本发明的各种试验资料：

一、生物活性试验：

1．材料和方法

1).受试物：

褪黑素胶囊由大连飞索集团提供，含量1mg/粒，临用时用蒸馏水溶解备用。安定片由赤峰制药厂提供。

2).动　物：

昆明种小鼠，由中国医科大学动物室提供，动物体重20±1g，雌雄各半。

2．试验方法：

取160只小鼠，随机分为16组，每组10只。第1组灌胃(ig)给予蒸馏水10ml/Kg，第2-4组分别灌胃(ig)投给褪黑素0.5、1、10mg/Kg，第5-7组分别灌胃(ig)投给安定1、5、25mg/Kg，　第8-10组分别灌胃(ig)投给褪黑素0.5mg/Kg和安定1、5、25mg/Kg，第11-13组分别灌胃(ig)投给褪黑素1mg/Kg和安定1、5、25mg/Kg，第14-16组分别灌胃(ig)投给褪黑素10mg/Kg和安定1、5、25mg/Kg，容量均为10ml/Kg，灌胃后30分钟，观察动物的活动状态，翻正反射是否消失及睡眠情况，实验室温度控制在27-28℃。

3.结　果

单给褪黑素胶囊的三组动物，给药半小时后活动减少，呈镇静状态，说明所用褪黑素的三种剂量均是催眠的最低剂量，给予安定的三种剂量组动物，活动逐渐减少，0.5mg/Kg组未发生睡眠，5和25mg/Kg组均出现睡眠（见表1），将褪黑素与安定组合投给各组后，各组均出现时间不等的睡眠状态，特别是褪黑素与安定均是最低剂量组动物也出现了翻正反射的消失，说明此组合确实增加了催眠效果。其他各组合物组动物的睡

眠时间明显比相同剂量下的安定组为长，其中效果最好的是褪黑素与安定1:25和10:25。经方差分析，各组合物组与对照组比较均有统计显著性，在组合物的两个因素中褪黑素的影响较大，但褪黑素的三种剂量中，1和10两种剂量之间差异不大。通过比较筛选褪黑素与安定的比例在1:5-25之间可获得较佳组合，1:5为最佳组合。

表1. 褪黑素与安定组合物对小鼠催眠时间的影响 ($\bar{X}\pm SD$)

组别	褪黑素剂量 (mg/Kg)	安定剂量 (mg/Kg)	睡眠时间 (分)
对照组	--	--	0
褪黑素	0.5	--	0
褪黑素	1	--	0
褪黑素	10	--	0
安　定	--	1	0
安　定	--	5	6.9±7.1
安　定	--	25	39.5±17.4
褪黑素＋安定	0.5	1	18.4±11.7
褪黑素＋安定	0.5	5	69.8±21.7
褪黑素＋安定	0.5	25	125.6±28.3
褪黑素＋安定	1	1	74.6±25.9
褪黑素＋安定	1	5	177.8±31.6
褪黑素＋安定	1	25	199.1±57.2
褪黑素＋安定	10	1	85.5±21.8
褪黑素＋安定	10	5	183.1±38.5
褪黑素＋安定	10	25	201.4±45.7

三、人体试用实验

从某医院年龄在30-45岁的睡眠不好的工作人员中，挑选志愿受试

者15人，经检查无任何其他疾病，实验过程中停用其他任何药物。每人于每日睡前口服褪黑素1mg与安定5mg，连续服用10天，10天后询问每人的主观反应。结果15人均反应用药后睡眠质量提高，作梦减少，无一人反应用药次晨有乏力或困倦现象。说明褪黑素和安定以较低剂量合用，达到了良好的睡眠效果，而且克服了安定的副作用。

毒性实验

1.方　法

将褪黑素和安定按比例混合，然后用蒸馏水溶解，配成尽可能高的浓度。取40只小鼠，雌雄各半，随机分为两组，分别给予最大浓度、最大允许体积的褪黑素安定混合物，给药剂量达到褪黑素10mg/Kg，安定50mg/Kg，尔后连续观察14天动物的行为变化及中毒表现。

2.实验结果

小鼠用药后，从15分钟开始，动物活动减少，呈睡眠状态，翻正反射消失约5小时，尔后逐渐恢复正常，此后至14天，未见其他任何改变。提示此组合物在正常剂量下应用是安全的。